United States Court of Appeals for the Federal Circuit

GENENTECH, INC., INTERMUNE, INC.,
Plaintiffs-Appellants

v.

SANDOZ INC., LEK PHARMACEUTICALS, D.D.,
Defendants-Appellees

2022-1595

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-00078-RGA, Judge Richard G. Andrews.

Decided: December 22, 2022

DARALYN JEANNINE DURIE, Durie Tangri LLP, San Francisco, CA, argued for plaintiffs-appellants. Also represented by KATHLEEN GERSH, RYAN NEIL HAGGLUND, WARREN K. MACRAE, MARK EDWARD WADDELL, Loeb & Loeb LLP, New York, NY; DAN LIU, Los Angeles, CA.

WILLIAM M. JAY, Goodwin Procter LLP, Washington, DC, argued for defendants-appellees. Also represented by EDWINA CLARKE, EMILY L. RAPALINO, DARYL L. WIESEN, Boston, MA; NATASHA ELISE DAUGHTREY, Los Angeles, CA.

Before NEWMAN, LOURIE, and PROST, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LOURIE.

Circuit Judge NEWMAN dissents without opinion.

LOURIE, *Circuit Judge*.

Genentech, Inc. and InterMune, Inc. (collectively, "Genentech") appeal from a decision of the United States District Court for the District of Delaware holding that: (1) the claims of its Liver Function Test ("LFT") patents[1] are unpatentable as obvious, (2) sale of Sandoz Inc.'s and Lek Pharmaceuticals, D.D.'s (collectively, "Sandoz's") generic product would not induce infringement of the LFT patents, and (3) sale of Sandoz's generic product would not directly infringe Genentech's Drug-Drug Interaction ("DDI") patents.[2] *See Genentech, Inc. v. Sandoz, Inc.*, No. 19-0078, 2022 WL 842957 (D. Del. Mar. 22, 2022) ("*Decision*"). We affirm.

BACKGROUND

Pirfenidone is a drug used to treat idiopathic pulmonary fibrosis ("IPF"). IPF is a chronic, irreversible lung disease. There is no cure for IPF and patients living with the disease face an average survival of two to five years. There are currently two drugs that have been approved by the FDA for the treatment of IPF, pirfenidone and nintedanib. Approximately half of the patients on treatment for IPF are prescribed pirfenidone, and the other half are prescribed nintedanib. The major differences between the drugs center on side effects and metabolism.

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[1] U.S. Patents 7,566,729 (the "'729 patent"), 7,635,707 (the "'707 patent"), 8,592,462 (the "'462 patent"), and 8,609,701 (the "'701 patent").

[2] U.S. Patents 7,816,383 (the "'383 patent") and 8,013,002 (the "'002 patent").

Pirfenidone was first studied as an investigational new drug in 1973. Development rights to pirfenidone were sold to Shionogi for Japan, South Korea, and Taiwan, and to InterMune for the rest of the world. In 2004, the United States Food and Drug Administration ("FDA") granted pirfenidone orphan drug status for treatment of patients with IPF. In 2014, pirfenidone was approved to treat IPF in the U.S. as Esbriet®, sold by Genentech.

Sandoz submitted two Abbreviated New Drug Applications ("ANDAs") seeking approval from the FDA to market a generic version of pirfenidone. Genentech then brought this Hatch-Waxman suit, asserting that Sandoz's generic product would induce the infringement of its LFT and DDI patents. The asserted patents do not claim pirfenidone itself, or the use of pirfenidone to treat IPF. Instead, the patents claim methods for managing certain side effects when using pirfenidone to treat IPF.

I. LFT Patents

The LFT patents are directed to methods for administering pirfenidone to a patient who has exhibited abnormal biomarkers of liver function in response to pirfenidone administration. The asserted claims in these patents recite various options, including: (1) temporarily reducing the dose of pirfenidone and then returning to the full dose, (2) maintaining the full dose of pirfenidone, (3) reducing the dose of pirfenidone, (4) discontinuing pirfenidone for a week and then returning to the full dose, and (5) discontinuing pirfenidone for a week and then returning to a reduced dose.

The claims of particular interest in this appeal are dependent claims. Therefore, for ease of understanding, we incorporate the parent claims into the claims that are asserted. The distinctions between the specific claims are not argued, so we recite the asserted claims as a group.

Asserted claim 9 of the '729 patent reads as follows:

> The method of claim 1 [*administering pirfenidone to treat a patient with IPF, said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising*
>
> *(a) administering to said patient pirfenidone at doses lower than 2400 mg/day for a time period, followed by*
>
> *(b) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day*], wherein said one or more biomarkers of liver function comprise alanine transaminase and aspartate transaminase.

'729 patent at col. 12 ll. 13–20, 48–50.

Asserted claim 6 of the '707 patent recites:

> The method of claim 1 [*administering pirfenidone to treat a patient with IPF, said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising*
>
> *(a) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day*], wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase.

'707 patent at col. 18 ll. 24–29, 42–44.

Asserted claim 14 of the '707 patent recites:

> The method of claim 7 [*administering pirfenidone to treat a patient with IPF, said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising*

> *(a) administering to said patient pirfenidone at doses of 1600 mg/day or 1602 mg/day*], wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase.

Id. at col. 18 ll. 45–50, col. 20 ll. 1–3.

Asserted claim 12 of the '462 patent recites:

> The method of claim 3 [*administering pirfenidone to treat a patient with IPF, said patient having exhibited an increase of about 2.5-fold to about 5-fold, compared to the upper limit of normal, in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 2400 mg/day or 2403 mg/day*] further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

'462 patent at col. 18 ll. 51–59, col. 19 ll. 33–36.

Asserted claim 28 of the '462 patent recites:

> The method of claim 26 [*administering pirfenidone to treat a patient with IPF, said patient having exhibited a Grade 2 abnormality in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second*

> *administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day*] further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

Id. at col. 20 ll. 35–42, 48–51.

Lastly, asserted claim 19 of the '701 patent recites:

> The method of claim 1 [*treating a patient in need of pirfenidone and suffering from a Grade 2 abnormality in a liver function biomarker selected from the group consisting of alanine transaminase (ALT) and aspartate transaminase (AST) and wherein the abnormality occurs after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient at doses of at least 1600 mg/day or 1602 mg/day*] wherein the patient suffers from idiopathic pulmonary fibrosis.

'701 patent at col. 18 ll. 33–41, col. 20 ll. 18–19.

Sandoz's proposed label includes, under the sub-heading "Dosage Modification due to Elevated Liver Enzymes," the following guidance for patients exhibiting Grade 2 liver enzyme elevations, depending upon whether they are asymptomatic or symptomatic:

> Dosage modifications or interruptions may also be necessary when liver enzyme and bilirubin elevations are exhibited. For liver enzyme elevations, modify the dosage as follows:

> If a patient exhibits >3 but ≤5 x the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting pirfenidone tablets therapy:
>
> - Discontinue confounding medications, exclude other causes, and monitor the patient closely.
> - Repeat liver chemistry tests as clinically indicated.
> - *The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re-titration to the full dosage as tolerated.*

J.A. 16750 (emphasis added).

The parties agree that Sandoz's label recommends using pirfenidone for the treatment of IPF and includes treatment instructions for patients exhibiting Grade 2 elevations in ALT and/or AST. The parties disagree over whether the third bullet point from the asymptomatic Grade 2 elevations sub-section induces use of any of the doses recited in the asserted claims.

At the district court, Sandoz alleged that (1) the LFT asserted claims would have been obvious over Azuma,[3] the Pirespa® label,[4] and known, standard medical practices;

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[3] Azuma et al., *Double-blind, Placebo-controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis*, 171 Am. J. of Respiratory & Critical Care Med. 1040 (2005) (J.A. 16624–31).

[4] Shionogi & Co., Ltd., Pirespa® Tablets 200 mg (2008) (J.A. 16550–54).

and (2) there was no specific intent for induced infringement.

Azuma reports on a pirfenidone clinical trial and states that "[f]or [patients experiencing] an adverse event of Grade 2 or worse," "the dosage of [pirfenidone] was reduced in a stepwise manner" for as long as symptoms persisted. J.A. 16626. Azuma adds that "[w]hen the adverse event of Grade 2 or worse persisted or increased despite reducing the dosage . . . [pirfenidone] was discontinued." *Id.* Azuma also lists "[e]levation of [AST]" among the "adverse events" observed in study patients. J.A. 16629.[5]

The Pirespa® label discloses a pirfenidone tablet for the treatment of IPF. Section 3(1) of the label states that "hepatic function disorders accompanied by increased AST (GOT), ALT (GPT), etc. and jaundice may occur and result in hepatic failure." J.A. 16551. The label instructs that "[i]f any abnormalities are observed, administration should be discontinued . . . ." *Id.* Section 3(2) contains a table, and next to "hepatic," the table lists, "AST (GOT), increased" and "ALT (GPT), increased." *Id.*

The district court began its analysis by noting that the parties "agree that Sandoz's label recommends using pirfenidone for the treatment of IPF and includes treatment instructions for patients exhibiting Grade 2 elevations in ALT and/or AST." *Decision* at *7. The court then recognized that the label contained explicit dosing instructions for patients experiencing Grade 2 elevations in AST or ALT describing: (1) maintaining the dose, (2) reducing the dose, (3) reducing the dose followed by re-titration to the full dose as tolerated, (4) interrupting the dose followed by re-titration to the full dose, and (5) discontinuing

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[5] Azuma refers to "Elevation of GOT." J.A. 16629. As the district court found, and the parties do not dispute, GOT is another name for AST. *Decision* at *11 n.7.

pirfenidone. The court found that four of the five dose modification options provided in the label were covered by the asserted claims. However, the court found that Sandoz did not infringe the LFT patents because there was no specific intent for induced infringement. Specifically, the portion of the label that referred to infringing uses did not recommend any of the infringing uses, but rather, merely described them.

The district court also held that the asserted LFT claims are unpatentable as obvious in light of Azuma, the Pirespa® label, and standard medical practice disclosed in the prior art. The court found that a skilled artisan reading Azuma would have concluded that the majority of patients exhibiting Grade 2 AST elevations could be treated with the study's dose reduction and reescalation protocol. The court also found that the Pirespa® label disclosed dose reduction as an option for patients with elevated liver enzymes. The court found that the Pirespa® label distinguished between increased ALT/AST accompanied by jaundice, and increased ALT/AST alone. For the former, the court found that the label instructed discontinuation, whereas for the latter, the label instructed dose reduction or discontinuation as necessary. Lastly, the court found that standard medical practice established that dose reductions, interruptions, and rechallenging were well known strategies for treating patients exhibiting Grade 2 elevations of liver enzymes while taking other drugs.

II. DDI Patents

The DDI patents are directed to methods for avoiding adverse interactions between pirfenidone and fluvoxamine. Fluvoxamine is a strong CYP1A2 inhibitor, which means it can interfere with normal drug metabolism by inhibiting the ability of certain CYP enzymes to metabolize the drug, resulting in "supratherapeutic" levels of an unmetabolized drug in the body. *See Decision* at *4. This can cause adverse events. Pirfenidone is highly susceptible to drug-

drug interaction with CYAP1A2 inhibitors. The three asserted DDI claims involve methods for administering pirfenidone to a patient taking fluvoxamine by either discontinuing fluvoxamine or modifying the dose of pirfenidone and continuing fluvoxamine. Similar to the LFT claims, the distinctions between the specific DDI claims are not argued, so we treat them all as a group.

Asserted claim 6 of the '383 patent recites:

> The method of claim 5 [*administering pirfenidone therapy to a patient in need thereof, comprising first discontinuing administration of fluvoxamine to avoid an adverse drug interaction with pirfenidone, and then administering to the patient a therapeutically effective amount of pirfenidone*], wherein the patient has [IPF].

'383 patent at col. 19 ll. 25–29, 30–31.

Asserted claim 3 of the '002 patent recites:

> The method of claim 2 [*administering pirfenidone and fluvoxamine concurrently to a patient in need thereof comprising administering a therapeutically effective amount of fluvoxamine to the patient and administering a therapeutically effective amount of pirfenidone to the patient, wherein the amount of the pirfenidone is about 801 mg/day, wherein the pirfenidone is administered three times per day*] wherein the patient has [IPF].

'002 patent at col. 19 ll. 14–19, col. 20 ll. 15–16.

Lastly, asserted claim 9 of the '002 patent recites:

> The method of claim 8 [*providing pirfenidone therapy to a patient in need thereof comprising titrating the dosage of pirfenidone administered to the patient downward from a dose of*

> *about 2400 mg/day, while co-administering fluvoxamine, wherein the dose of pirfenidone is reduced by about 1600 mg/day, wherein the pirfenidone is administered three times per day*] wherein the patient has [IPF].

Id. at col. 20 ll. 6–10, 13–16.

Sandoz's proposed label warns about potential drug-drug interactions with fluvoxamine in three places. First, under the "Drug Interactions" sub-heading of the label's "Highlights of Prescribing Information," the label states "[d]iscontinue fluvoxamine prior to administration of pirfenidone or reduce [pirfenidone] to 267 mg three times a day," for a total of 801 mg/day. J.A. 16749. Second, in Section 2.4, "Dosage Modification due to Drug Interactions," under the sub-heading, "Strong CYP1A2 Inhibitors (e.g., fluvoxamine, enoxacin)," the label states "Reduce pirfenidone tablets to 267 mg three times a day (801 mg/day)." J.A. 16751. Finally, in Section 7.1, "CYP1A2 Inhibitors," under the sub-heading, "Strong CYP1A2 Inhibitors," the label states:

> The concomitant administration of pirfenidone and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to pirfenidone *[see Clinical Pharmacology (12.3)]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of pirfenidone and avoided during pirfenidone treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of pirfenidone as needed *[see Dosage and Administration (2.4)]*.

J.A. 16753 (emphasis in original).

At the district court, Sandoz argued that there was insufficient evidence of direct infringement. The court agreed and added that the language in Sandoz's label that encourages, recommends, or promotes an infringing use without any additional evidence showing such an infringing use will in fact occur, is insufficient for a finding of direct infringement. The court elaborated and stated that Genentech had not shown that any patient would be prescribed both pirfenidone and fluvoxamine such that the methods of the DDI patents would even be relevant. The court added that even if an IPF patient were prescribed fluvoxamine, a physician would likely choose a non-infringing treatment adjustment over any of the claimed methods.

Genentech appealed the district court's holdings that the asserted claims in the LFT patents would have been unpatentable as obvious, that sale of Sandoz's product would not induce infringement of the LFT patents, and that Sandoz's product would not directly infringe the DDI patents. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

After a bench trial, we review the district court's judgment for legal error or clearly erroneous findings of fact. *Grunenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019). Infringement, including induced infringement, is a question of fact that we review for clear error. *Id.*

Whether a claim is invalid as obvious is a question of law, based on underlying factual determinations. *E.g.*, *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2019). The ultimate legal question is reviewed *de novo*, and the underlying factual determinations are reviewed for clear error. *Id.* at 1328. "Where there are two permissible views of the evidence, the fact-finder's choice between them cannot be clearly erroneous"; rather, a finding is clearly erroneous only when the reviewing

court is "left with a definite and firm conviction that the district court was in error." *Id.* (citations omitted).

To succeed on a theory of induced infringement in a Hatch-Waxman case, in which infringement is defined by filing an ANDA before the infringing product is marketed, the plaintiff is required to prove by a preponderance of the evidence (1) direct infringement, *i.e.*, if defendant's drug was "put on the market, it would infringe the relevant patent"; and (2) "that [defendant] possessed the specific intent to encourage another's infringement." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129–30 (Fed. Cir. 2018). Specific intent may be shown if the defendant's proposed label recommends, encourages, or promotes an infringing act. *See Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharms. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

I. LFT Patents

With respect to obviousness, Genentech argues that the district court improperly supplied missing claim limitations, read the prior art in ways that cannot be supported based on plain meaning, and failed to make any legal or factual findings with respect to claim 9 of the '729 patent and claim 12 of the '462 patent. Genentech asserts that neither Azuma nor the Pirespa® label literally discloses Grade 2 elevated liver enzymes or the claimed continued treatment of patients with pirfenidone. It adds that these elements are not within the knowledge of those skilled in the art. Genentech also argues that the court's analysis of the Pirespa® label is not entitled to deference, and should be reviewed *de novo*, because it involved no fact finding. Lastly, Genentech asserts that objective indicia of nonobviousness weighed in its favor because it showed skepticism regarding pirfenidone's efficacy and safety, as well as evidence of a long-felt and unmet need of treating patients following Grade 2 AST/ALT elevations.

Sandoz responds that the district court properly found that Azuma expressly disclosed reescalation of dosage after temporary dose reduction for patients with Grade 2 liver enzyme elevations. It adds that a skilled artisan could infer that patients with Grade 2 AST/ALT elevations were treated in accordance with the reduction and reescalation protocol for Grade 2 adverse events. Regarding the Pirespa® label, Sandoz argues that the court did not clearly err in interpreting the label to recommend discontinuing pirfenidone only for patients with elevated liver enzymes accompanied by jaundice and not for patients with elevated liver enzymes without jaundice.

With respect to the objective indicia of nonobviousness, Sandoz asserts that Genentech's evidence of skepticism did not relate to using the LFT methods to treat Grade 2 liver enzyme elevations. It further asserts that Genentech did not establish a long-felt and unmet need for continuing to treat patients with pirfenidone following a Grade 2 elevation.

Before reviewing the details of the district court's thorough analysis, it is worth noting our initial perception that, as the district court noted, varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot. The district court gave it careful scrutiny, however, as do we.

We agree with Sandoz that the district court did not err in its conclusion of obviousness. It properly held that the specific dose modifications claimed in the LFT patents would have been obvious over the disclosures in Azuma and the Pirespa® label, combined with well-known standard medical practices. Specifically, the court found that Azuma disclosed reescalation of dosage after temporary dose reduction for patients with Grade 2 or worse adverse events, and that liver enzyme elevations were included in the list of observed adverse events. The court added that

while Azuma "does not specify how many of these AST elevations were Grade 2 elevations," a skilled artisan could infer from the disclosure that patients with Grade 2 AST elevations were treated in accordance with the reduction and reescalation protocol for Grade 2 adverse events. *See Decision* at *11. These findings are not clearly erroneous.

With respect to the Pirespa® label, it is well established that what the prior art teaches is a factual question we review for clear error. *See Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1364 (Fed. Cir. 2022). The standard of review does not change when the district court is assessing documentary evidence rather than testimony. *See* Fed. R. Civ. P. 52(a)(6) & advisory committee's note (1985) (explaining that bench trial findings are reviewed for clear error whether interpreting documentary or oral evidence). The scope and content of the prior art are characterized as factual findings.

Moving to the merits, Genentech fails to identify any clear error in the district court's interpretation of the Pirespa® label. Genentech argues that the Pirespa® label instructs prescribers to look to Section 3(1) for any patients with increased AST/ALT, and not only for patients suffering from jaundice. It adds that Section 3(1)'s language that "[i]f any abnormalities are observed, administration should be discontinued" encompasses an increase in AST or ALT without jaundice. *See* J.A. 16551. Genentech's interpretation is not persuasive.

Section 2(3), on which Genentech relies, states that "[h]epatic function disorders accompanying increased AST (GOT), ALT (GPT), etc. and jaundice may occur," and refers clinicians to Section 3(1) which employs the same language and recommends discontinuation. Furthermore, as the district court found, Section 3(1)'s instruction for "any abnormalities" applies to only the particular abnormalities mentioned previously in that instruction—*i.e.*, elevated AST/ALT with jaundice. *See Decision* at *12. Genentech's

interpretation would also create a conflict, whereby Section 3(1) would instruct a clinician to discontinue treatment upon observing elevated AST/ALT, while Section 3(2) would allow dose reduction or discontinuation for the same event.

Contrary to Genentech's assertion, the district court's interpretation of Azuma and the Pirespa® label also relied on extensive record evidence. That evidence illustrated that standard medical practice at the time was not to discontinue medical treatment with pirfenidone or other drugs for patients experiencing Grade 2 liver enzyme elevations. This evidence included expert testimony as well as FDA guidance. *See* J.A. 7387–89; 8488–89.

Lastly, the district court did not err by not making specific findings for claim 9 of the '729 patent and claim 12 of the '462 patent. These claims relate to dose reescalation after dose reduction (claim 9 of the '729 patent) and dose interruption (claim 12 of the '462 patent). The court expressly found that Azuma disclosed that "'[i]f the adverse event had resolved or decreased with [a] reduction in dose,' the patient's dose was increased back to the original amount." *Decision* at *11 (citing J.A. 16626). Azuma also states that for individuals with a "Grade 2 or worse" event, the dose was "reduced in a stepwise manner: from 9 tablets per day to 6 tablets per day." J.A. 16626. It adds that if the adverse event persisted, then "the study medication was discontinued and patients observed." *Id.* The Pirespa® label states that "[w]hen gastrointestinal disorder, etc. occurs, dose reduction or drug withdrawal is considered as necessary" and that "[w]hen the symptom is relieved, it is desirable that the dose is gradually increased to [the original amount]." J.A. 16550. These two references discuss the same reescalation and dose reduction techniques encompassed by claim 9 of the '729 patent and claim 12 of the '462 patent. Therefore, these two references would have rendered those claims obvious, and the court did not err in

not discussing its factual findings with respect to those claims specifically.

With respect to the objective indicia of nonobviousness, the district court properly found Genentech's evidence unpersuasive. "[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness." *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1371 (Fed. Cir. 2010). Here, Genentech's evidence of objective indicia does not outweigh Sandoz's affirmative case of obviousness.

First, Genentech did not provide evidence showing skepticism regarding rechallenging patients with Grade 2 liver enzyme elevations compared to patients with more serious Grade 3 or higher elevations. Thus, Genentech's evidence does not establish skepticism for the claimed methods. Second, in its argument of long-felt but unmet need, Genentech cites evidence that one expert at trial "ha[s] seen many patients with [G]rade 2 elevations" and that the Esbriet® label states that "dose modification or treatment discontinuation" can reverse liver damage in some patients with elevated liver enzymes. J.A. 7293, 16517–18; *see also* Appellant's Br. at 59. These two pieces of evidence, however, do not establish any long-felt, unmet need for the claimed methods. Furthermore, FDA guidance recommended not dropping patients with Grade 2 elevations from clinical trials. J.A. 7383. Thus, Genentech has not demonstrated that the court clearly erred with respect to its factual findings regarding skepticism and long-felt, unmet need.

For these reasons, we affirm the court's holding that the asserted claims in the LFT patents would have been obvious over Azuma and the Pirespa® label, combined with well-known, standard medical practices. The asserted claims in the LFT patents do not represent the invention of a new drug, nor do they recite a novel application of an existing drug. Instead, these claims recite adjusting doses in

the presence of side effects, which clinicians routinely do, and which would have been obvious in view of the prior art.

In light of our invalidity holding, we need not review the court's infringement findings.

II. DDI Patents

Turning to the DDI patents, Genentech argues that the district court erred in finding that the asserted claims were not infringed. Specifically, Genentech asserts that the court erred in concluding that Sandoz's proposed label, which encourages, recommends, and promotes infringement, is not dispositive. It adds that, even if other evidence could overcome the label's instruction to infringe, here, there was no evidence to negate the label's language. Instead, Genentech asserts, the court treated the label as having no evidentiary force and faulted Genentech for failing to adduce more evidence of infringement. Lastly, Genentech argues that if we reverse on the issue of direct infringement, we should also find that Sandoz had the specific intent to induce infringement.

Sandoz responds that the district court did not clearly err in weighing the relevant evidence, including the label's instruction and physician practice. It adds that while Genentech was not required to show an actual incident of direct infringement by a physician, past conduct was relevant to what would happen in the future. Lastly, Sandoz argues that if we find direct infringement, we should allow the lower court to decide whether there was specific intent to induce infringement in the first instance.

We agree with Sandoz. It is true that although the Hatch-Waxman Act provides that the filing of an ANDA before a patent covering a compound or a use expires meets the technical jurisdictional requirement of infringement, that is not the same as the direct infringement that serves as a predicate for finding induced infringement. *See* 35 U.S.C. § 271(e)(2)(A) (filing an ANDA before a patent

expires is "an act of infringement"); *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1568–69 (Fed. Cir. 1997) ("The plain language of [§ 271(e)(2)(A)] does not alter a patentee's burden of proving infringement . . . ."). Infringement still requires a finding that accused subject matter would meet the terms of a claim.

Here, Genentech fails to identify any legal error or clear factual error in the district court's direct infringement analysis. In order to prove direct infringement, Genentech must show that "if a particular drug were put on the market, it would infringe the relevant patent." *Vanda*, 887 F.3d at 1129–30. Determining what will, or would, happen when a product enters the market requires "consideration of all the relevant evidence," including the proposed label's instructions and physician practice. *Ferring v. Watson Lab'ys*, 764 F.3d 1401, 1408 (Fed. Cir. 2014); *see also Glaxo*, 110 F.3d at 1570 (stating that "[t]he relevant inquiry [for direct infringement] is whether the patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product," and further concluding that "the district court properly considered the ANDA itself, the materials submitted by Novopharm to FDA, and the other pertinent evidence provided by the parties"). The court recognized that "a patentee does not need to prove an actual past instance of direct infringement by a physician to establish infringement in an ANDA case." *Vanda*, 887 F.3d at 1129–30. While this is correct, as Sandoz notes, past conduct is relevant to what will happen in the future.

We regularly consider evidence outside a proposed label in evaluating whether a product will be used in a way that directly infringes method claims. In *Eli Lilly*, for example, we relied on "[t]he product labeling, combined with [] testimony [discussing physicians' general practices]" to conclude that there was sufficient evidence "that physicians condition . . . treatment on" the patients' performance of the patented method, thereby satisfying the

requirements for proving direct infringement. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364–68 (Fed. Cir. 2017). Similarly, in *Takeda*, we looked at evidence outside the label to determine whether the plaintiffs had proven direct infringement of certain drug-drug interaction patents. We considered the dosage form and size of the defendant's product in determining that plaintiffs had failed to prove that a patient would take a dose equal to half that size, as required by the drug-drug interaction claims at issue. *See Takeda*, 785 F.3d at 634–35. And we also considered, with respect to different method patents requiring concomitant administration of two drugs, the fact that "physician experts declared that they try to and can easily avoid concomitant administration of the drugs." *Id.* at 635. Although the label in *Takeda* did not recite the specific claimed doses at issue in that case, our analysis did not hinge on that.

Lastly, *Vanda* involved conducting a genotyping assay to determine (1) whether a patient is a poor metabolizer of iloperidone; and (2) if so, administering a lower dose. The district court found that the generic label directed the infringing method, including the genotyping test. *See Vanda Pharms. Inc. v. Roxane Lab'ys, Inc.*, 203 F. Supp. 3d 412, 432–33 (D. Del. 2016). The defendant argued that the label was not determinative because physicians did not actually administer a genotyping test before making a dosing determination. *Id.* at 433. However, because plaintiffs had introduced evidence that physicians did genotype their patients, the court rejected defendant's argument. *Id.* On appeal, we affirmed and cited *Ferring* for the proposition that "[t]he infringement determination is . . . based on consideration of all the relevant evidence." *Vanda*, 887 F.3d at 1130 (citing *Ferring*, 764 F.3d 1408).

Here, as in *Eli Lilly* and *Takeda*, the district court did not clearly err by considering all the relevant evidence, including Sandoz's proposed label and physician practice. Sandoz presented evidence of how pirfenidone would be

prescribed in practice, including testimony from physicians that, in their decades of treating IPF patients, they had never prescribed pirfenidone to an IPF patient taking fluvoxamine; and were they to find themselves in that position, they would choose a noninfringing response—*i.e.*, prescribing nintedanib instead. *See Decision* at *16; *see also* J.A. 7196, 7269, 7270–71. The court did not clearly err by considering physician evidence, weighing it against the language in Sandoz's proposed label, and finding that Genentech failed to prove direct infringement. Genentech's arguments to the contrary are unavailing.

Genentech argues that the DDI instructions must be important because the FDA insisted on including them in the label. However, Genentech cites no evidence to support its speculation. Even if the FDA had been concerned about the possibility that a patient may be treated with both pirfenidone and fluvoxamine, that does not establish by a preponderance of the evidence that if Sandoz's drug "were put on the market, it would infringe" the asserted DDI claims. *See Vanda*, 887 F.3d 1129–30 (citation omitted). Second, Genentech's argument that fluvoxamine could be used to treat COVID-19, and that at least one patient living with IPF could be prescribed both fluvoxamine and pirfenidone was properly rejected by the district court as speculative. Third, Genentech argues that the district court improperly credited Sandoz's physician evidence. Specifically, it argues that if an IPF patient needed fluvoxamine, instead of a doctor prescribing nintedanib to treat their IPF, the doctor could prescribe pirfenidone and an alternative to fluvoxamine. However, as Sandoz's expert stated, a pulmonologist prescribing pirfenidone would not be able to alter another physician's prescription of fluvoxamine or take over that aspect of the patient's treatment. Therefore, the pulmonologist would prescribe nintedanib to be taken in conjunction with the patient's preexisting prescription of fluvoxamine.

Weighing all the evidence, the district court did not clearly err in finding that Genentech had not met its burden to show that if Sandoz's drug were put on the market, it would directly infringe the asserted claims of the DDI patents which require use of both pirfenidone and fluvoxamine. In light of our finding of no direct infringement, we need not reach the issue of whether Sandoz possessed the specific intent to induce infringement of the asserted claims in the DDI patents.

CONCLUSION

We have considered Genentech's remaining arguments but find them unpersuasive. For the foregoing reasons, we conclude that the district court properly held that the asserted claims in the LFT patents would have been obvious over the prior art and standard medical practice, and it did not clearly err in finding that Sandoz's generic product would not directly infringe the asserted claims in the DDI patents.

AFFIRMED